Claim 23 (Amended). A method according to claim 19, in which the compound is designed or selected to have a K_1 of less than 10^{-9} M.

Please add the following new claims.

Claim 54. (New) A method according to claim 1, wherein the testing in (v) is carried out *in vitro*.

Claim 55. (New) A method according to claim 54, wherein the testing is performed by a high throughput assay.

Claim 56. (New) A method according to claim 1, wherein the testing in (v) is carried out *in vivo*.

REMARKS

Reconsideration of the subject application is respectfully requested in view of the amendments above and the comments below.

Claims 1-52 are pending in the present application. Claims 24-52 have been withdrawn from consideration. Accordingly, claims 1-23 are presented for examination on the merits.

Claims 1-13, 15 and 17-23 were amended to more clearly define the active steps of the claimed methods. No new matter is added by these

I. Restriction Requirement

The Restriction Requirement has been made final and claims 24-52 have been withdrawn from consideration. The Examiner states that each of the steps of the methods set forth in Groups I-III and VII is different and distinct. For example, the Examiner states that the special technical feature of the method of claims 1-23 is compound design and that of claims 24-29 is compound identification using computer assistance. The Examiner concludes, therefore, that these two groups of claims do not relate to a single general inventive concept.

Applicants respectfully disagree with the Examiner's conclusion.

The steps set forth in Claims 1-23 are basically the same as those used in claims 24-29, the significant difference being that the method of the latter set of claims employs the use of a computer to select the desired compounds and in the former set of claims, no particular device is recited for selecting compounds that meet the claim criteria. The method set forth in both sets of claims involves assessing the stereochemical complementarity between the compound to be selected and a topographic region of the EGF molecule shown in Figure 6; and once such a compound is obtained, either by use of computer modeling and selection from a computer databank (Claims 24-29) or by any means of identifying the desired compound (Claims 1-23), the selected compound is tested to determine whether it affects the activity of the EGF molecule. Clearly, the special technical feature of these claims is the provision of the three dimensional structure of the EGF molecule so that it may be used to design or select proteins that interact with its active sites.

The use of a computer to identify proteins is known in the art, as is the use of visual scanning or modeling. But, neither computer scanning, nor visual scanning or other means of selecting the compounds is claimed. The claims are directed to the use of the novel three dimensional structure of the EGF molecule to design or select compounds that interact with it and thereby affect EGF activity. Thus, there is inventive unity between the claims of at least Groups I and II and as such, claims 24-29 should be examined together with claims 1-23.

Accordingly, it is respectfully submitted that the Restriction Requirement, as far as it relates to Claims 1-23 and Claims 24-29 is improper and should be withdrawn.

II. Rejection of Claims 1-23 Under 35 U.S.C. § 101

It is respectfully submitted that the amendments to the claims render the rejection of claims 1-23 under 35 U.S.C. § 101 moot.

III. Rejection of Claims 1-23 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendments to the claims render the formal grounds of rejection moot. It is also pointed out that claims 8 and 11 were amended to recite "a" hinge in place of "the " hinge even though the hinge region between the L2 and S1 domains and between the L2 and S2 is inherently presently in the EGF molecule. As such, this amendment to the claim does not alter the scope of the claim.

IV. Rejection of Claims 1-23 Under 35 U.S.C. § 103(a)

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph over Garrett, et al. (Nature, July 1998), in view of Kuntz et al. (J. Mol. Biol. 1982) and Goodford ((J. Med. Chem. 1985). The Examiner relies on Garrett et al. as teaching the crystal structure of of the EGF receptor (EGRF); Kuntz et al. is relied on as providing motivation for designing compounds by geometric fit that fit or complement structural matches of ligands or receptors; and Goodford is relied on as teaching the use of a known protein for molecular design of probes with the most favorable energy levels. The Examiner concludes that it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to have used the EGF receptor structure of Garrett et al. for the design of EGFR binding ligands by methods disclosed by Kuntz et al. The Examiner also states that it would have been obvious to have included the energy modeling features of the methods of Goodford.

This rejection is respectfully traversed as follows.

Garrett et al. was published July 23, 1998, which is after the effective priority date of the subject application (May 29, 1998). As such, Garrett, et al. is not prior art to the present invention. Accordingly, it is respectfully submitted that this reference is improperly applied and should be removed as prior art.

Moreover, Garrett et al. disclose the crystal structure of type-1 IGF-1R, a molecule that is characterized as "closely related" to the EGFR family, but this reference does not provide the crystal structure of EGFR, as averred by the Examiner. Moreover, Garrett et al. clearly point out that the structure of IGF-1R differs significantly from that of EGFR in that the latter is comprised of four domains (L1, L2, S1 and S2), whereas

IGF-1R contains only three domains. As can be seen from the crystal structure of EGFR provided in Figures 3, 4 and 5 of the subject application, the structure of EGFR is significantly different from that of IGF-1R, albeit some structural similarities do exist. Moreover, Garrett et al. point out that members of the IR family are different from most other cell-surface receptors, i.e., EGFR, in that the IR subfamily pre-exists as disulfide-linked primers. EGFR on the other hand, dimerizes upon binding with its ligand. Thus, Garrett et al.'s disclosure of the IGF-1R structure neither discloses nor suggests how the EGF receptor binds ligand.

Garrett et al. make no suggestion that the crystal structure of IGF-1R suggests how the EGF receptor might interact with its receptor. The Examiner has taken an enormous leap of faith, based primarily on hindsight knowledge, and concluded that the known structure of IGF-1R provides sufficient knowledge of the EGF receptor to render obvious the design or selection of EGFR ligands that affect the activity of . Clearly, it does not.

Applicants determined the crystal structure of the EGF receptor by alignment of known EGFR sequence and structure with that of IGF-1R and where the similarities fell off, e.g., domain S2 of EGFR (which does not exist in IGF-1R), applicants utilized data obtained from several EGFR mutants to determine the role of several regions of the EGF receptor. Clearly, the stereochemical structure of EGFR set forth in the claims was neither disclosed nor suggested by Garrett et al.

The deficiencies of Garrett et al. are not compensated for by Kuntz et al. and Goodford, which also fail to teach or suggest the crystal structure of the EGF receptor. These references merely disclose that it is possible to design binding ligands once the

structure of a receptor molecule is known. However, without knowledge of the structure of the receptor, such modeling is neither possible, nor obvious. Since the structure of the EGF receptor was not known prior to the claimed invention, it would not have been obvious to design molecules that bind to the EGF receptor on the basis of the combined prior art.

Accordingly, the rejection of claims 1-23 under 35 U.S.C. § 103(a) over the cited arrt is respectfully traversed.

V. Objection to Claims 5-23

The Examiner objects to claims 5-23 under 37 C.F.R. § 1.75(c) as allegedly being in improper format because a multiply dependent claim cannot depend from another multiply dependent claim.

This objection is respectfully traversed as follows.

Multiple dependencies of claims 9-13, 15, 17-19 and 21 were deleted in the Preliminary Amendment filed November 29, 2000. As such, none of claims 5-23 is multiply dependent. Therefore, this objection is moot.

It is respectfully submitted that the present application, as amended above, is in condition for allowance, an early notification thereof being earnestly solicited.

Please charge any shortage of fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit Account.

Respectfully submitted,

McDERMOTT, WILL & EMERY

Date: 6/11/2002

By: Daniel Bucca 42368
for Judith L. Toffenetti
Registration No. 39,048

600 13th Street, N.W. , Suite 1200
Washington, D.C. 20005-3096
Date: June 11, 2002 RLP/JLT/rp
Telephone: 202-756-8000
Facsimile: 202-756-8087

WDC99 592945-1.050179.0086

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 11, line 13 has been amended as follows:

Figure 6: Coordinates of the two models of the EGF receptor extracellular domain. The first model (6A-1 through top half of 6A-32) consists of the domains L1 and S1. The second model (6A-32 (bottom half) through 6B-31) consists of the domains L2 and S2. The coordinates are in relation to a Cartesian set of orthogonal axes. The L1, S1 and L2 domains of the EGF receptor models have been superimposed on the crystal structure of the IGF-1 receptor domains L1, cysteine-rich domain and L2. The final column contains the number 20, 40 or 60, depending on whether the residue containing the atom is judged to be well-modeled, have a moderate possibility of error, or is likely to be inaccurate, respectively.

IN THE CLAIMS:

Please amend the claims 1-13 and 15, 17-23 and add new claims 54-56 as follows:

Claim 1 (Amended). A method of designing or selecting a compound which binds to a molecule of the EGF receptor family and modulates an activity mediated by the molecule, which method comprises [the step of]

(A) assessing the stereochemical complementarity between the compound and a topographic region of the molecule, wherein the molecule [is characterized by] comprises

(i) amino acids 1-621 of the EGF receptor positioned at atomic coordinates substantially as shown in Figure 6;

(ii) one or more subsets of said amino acids related to the coordinates shown in Figure 6 by whole body translations and/or rotations;

(iii) amino acids present in the amino acid sequence of a member of the EGF receptor family, which form an equivalent three-dimensional structure to that of the receptor site defined by amino acids 1-621 of the EGF receptor positioned at atomic coordinates substantially as shown in Figure 6;

(B) obtaining a compound which possesses stereochemical complementarity to a topographic region of the molecule; and

(C) testing the compound for its ability to modulate an activity mediated by the molecule.

Claim 2 (Amended). A method as claimed in claim 1 in which the compound is selected to complement the topographic region of the molecule is defined by amino acids 1-475 of the EGF receptor positioned at atomic coordinates substantially as shown in Figure 6, or an amino acid sequence which forms an equivalent three-dimensional structure to that of the region defined by amino acids 1-475 of the EGF receptor positioned at atomic coordinates substantially as shown in Figure 6.

Claim 3 (Amended). A method as claimed in claim 1 in which the compound is selected to complement the topographic region of the molecule is defined by amino acids 313-621 of the EGF receptor positioned at atomic coordinates substantially as

shown in Figure 6, or an amino acid sequence which forms an equivalent three-dimensional structure to that of the region defined by amino acids 313-621 of the EGF receptor positioned at atomic coordinates substantially as shown in Figure 6.

Claim 4 (Twice Amended). A method as claimed in claim 1 in which the compound is designed or selected so as to complement the structure of a topographic region of the molecule as depicted in Figure 5.

Claim 5 (Twice Amended). A method as claimed in claim 1 in which the compound [has] is designed or selected to comprise structural regions able to make close contact with amino acid residues at the surface of the molecule lining [the] a groove region as depicted in Figure 7, Figure 8 or Figure 9.

Claim 6 (Twice Amended). A method as claimed in claim 1, in which the compound [has] is designed or selected to have a stereochemistry such that it can interact with both the L1 and L2 domains of the molecule.

Claim 7 (Twice Amended). A method as claimed in claim 1, in which the compound [interacts] is designed or selected to interact with the region of the L1 domain-S1 domain interface, causing an alteration in the positions of the L1 and S1 domains relative to each other.

Claim 8 (Twice Amended). A method as claimed in claim 1, in which the compound [interacts] is designed or selected to interact with [the] a hinge region between the L2 domain and the S1 domain causing an alteration in the positions of the L2 and S1 domains relative to each other.

Claim 9 (Twice Amended). A method as claimed in claim 1, in which the compound [interacts] is designed or selected to interact with the -sheet of the L1 domain causing an alteration in the position of the L1 domain relative to the position of the S1 domain or the L2 domain.

Claim 10 (Twice Amended). A method as claimed in claim 1, in which the compound [has] is designed or selected to have a stereochemistry such that it can interact with both the L2 and S2 domains of the molecule.

Claim 11 (Twice Amended). A method as claimed in claim 1, in which the compound [interacts] is designed or selected to interact with [the] a hinge region between the L2 domain and the S2 domains causing an alteration in the positions of the L2 and S2 domains relative to each other.

Claim 12 (Twice Amended). A method as claimed in claim 1, in which the compound [interacts] is designed or selected to interact with the -sheet of the L2 domain causing an alteration in the position of the L2 domain relative to the position of the S2 domain.

Claim 13 (Twice Amended). A method as claimed in claim 1 in which the compound [binds] is designed or selected to bind to a lower face containing the second -sheet of the L1 and/or L2 domains, wherein the structure of the face is characterized by a plurality of solvent-exposed hydrophobic residues.

Claim 15 (Twice Amended). A method as claimed in claim 1, in which the [stereochemical complementarity between the] compound [and the receptor site] is designed or selected to have a stereo complementarity with the receptor site of the molecule such that the compound has a K_d for the receptor site of less than 10^{-6} M.

Claim 17 (Twice Amended). A method as claimed in claim 1 in which the compound is designed or selected from or modified from [a known] test [compound] compounds identified from a data base.

Claim 18 (Twice Amended). A method according to claim 1, in which the compound [has] is designed or selected to have the ability to increase an activity mediated by a molecule of the EGF receptor family.

Claim 19 (Twice Amended). A method according to claim 1, in which the compound [has] is designed or selected to have the ability to decrease an activity mediated by a molecule of the EGF receptor family.

Claim 20 (Amended). A method according to claim 19, in which the molecule is designed or selected to have a stereochemical interaction with [between] the compound and the molecule [is adapted to prevent] that prevents the binding of a natural ligand of the receptor molecule to the receptor site.

Claim 21 (Twice Amended). A method according to claim 19, in which the compound [has] designed or selected to have a K_1 of less than 10^{-6} M.

Claim 22 (Amended). A method according to claim 19, in which the compound [has] is designed or selected to have a K_1 of less than 10^{-8} M.

Claim 23 (Amended). A method according to claim 19, in which the compound [has] is designed or selected to have a K_1 of less than 10^{-9} M.

Please add the following new claims.

Claim 54. (New) A method according to claim 1, wherein the testing in (v) is carried out *in vitro*.

Claim 55. (New) A method according to claim 54, wherein the testing is performed by a high throughput assay.

Claim 56. (New) A method according to claim 1, wherein the testing in (v) is carried out *in vivo*.